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Congenital Heart Block: Development of Late-Onset Cardiomyopathy, a Previously Underappreciated Sequela

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OBJECTIVES We report 16 infants with complete congenital heart block (CHB) who developed late-onset dilated cardiomyopathy despite early institution of cardiac pacing.

BACKGROUND Isolated CHB has an excellent prognosis following pacemaker implantation. Most early deaths result from delayed initiation of pacing therapy or hemodynamic abnormalities associated with congenital heart defects.

METHODS A multi-institutional study was performed to identify common clinical features and possible risk factors associated with late-onset dilated cardiomyopathy in patients born with congenital CHB.

RESULTS Congenital heart block was diagnosed in utero in 12 patients and at birth in four patients. Ten of 16 patients had serologic findings consistent with neonatal lupus syndrome (NLS). A pericardial effusion was evident on fetal ultrasound in six patients. In utero determination of left ventricular (LV) function was normal in all. Following birth, one infant exhibited a rash consistent with NLS and two had elevated hepatic transaminases and transient thrombocytopenia. In the early postnatal period, LV function was normal in 15 patients (shortening fraction [SF] = 34 ± 7%) and was decreased in one (SF = 20%). A cardiac pacemaker was implanted during the first two weeks of life in 15 patients and at seven months in one patient. Left ventricular function significantly decreased during follow-up (14 days to 9.3 years, SF = 9% ± 5%). Twelve of 16 patients developed congestive heart failure before age 24 months. Myocardial biopsy revealed hypertrophy in 11 patients, interstitial fibrosis in 11 patients, and myocyte degeneration in two patients. Clinical status during follow-up was guarded: four patients died from congestive heart failure; seven required cardiac transplantation; one was awaiting cardiac transplantation; and four exhibited recovery of SF (31 ± 2%).

CONCLUSIONS Despite early institution of cardiac pacing, some infants with CHB develop LV cardiomyopathy. Patients with CHB require close follow-up not only of their cardiac rate and rhythm, but also ventricular function. (J Am Coll Cardiol 2001;37:238–42) © 2001 by the American College of Cardiology

The incidence of congenital heart block (CHB) in the general population has been estimated to vary between 1/15,000 and 1/22,000 live-born infants (1). Heart block may be associated with maternal autoantibodies against SSA (Ro) or SSB (La) proteins (neonatal lupus syndrome, NLS) or secondary to specific cardiac malformations, e.g., atrioventricular (AV) discordance or polysplenia with AV canal defect. Heart block resulting from the NLS is most often identified between 18 and 28 weeks gestational age and is frequently permanent (2). Isolated CHB has an excellent prognosis following pacemaker implantation (3–5). In most series of patients with CHB, early death results from delayed initiation of pacing therapy or hemodynamic compromise from associated significant congenital heart disease.

Waltuck and Buyon (2) have assessed fetal and neonatal outcome in 55 children known to be autoantibody positive for SSA (Ro) or SSB (La) antigen. Seventeen, or 31%, of the children died during follow-up. Deaths were classified as either early or late. Early deaths occurred in the first month and were attributed to congestive heart failure (four

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Abbreviations and Acronyms
AV = atrioventricular
CHB = congenital heart block
NLS = neonatal lupus syndrome
SF = shortening fraction

patients), multiorgan failure (three patients), respiratory failure (two patients), stillbirth with CHB (one patient), and unknown causes (two patients). The causes of late death were congestive heart failure (three patients), pacemaker failure (one patient), and complications of pacemaker implantation (one patient).

Our purpose is to describe the clinical course of 16 infants with CHB who developed late-onset dilated congestive cardiomyopathy despite early institution of cardiac pacing. A multi-institutional study was performed to identify common clinical features and possible risk factors associated with late-onset dilated cardiomyopathy in patients born with congenital complete AV block.

METHODS

This study was a retrospective collaborative effort among ten pediatric cardiology institutions involved in the care of infants with congenital CHB who developed cardiomyopathy despite early implantation of a cardiac pacemaker. The participating centers and the number of contributed patients are as follows: Children's National Medical Center, Washington, DC (four patients); Medical College of South Carolina, Charleston, South Carolina (three patients); Wilhelmina Children's Hospital, Utrecht, Netherlands (two patients); Children's Hospital and Medical Center, Seattle, Washington (one patient); Children's Hospital of the King's Daughters, Norfolk, Virginia (one patient); Geisinger Clinic, Danville, Pennsylvania (one patient); Polyclinic Medical Center, Harrisburg, Pennsylvania (one patient); Rainbow Babies and Children's Hospital, Cleveland, Ohio (one patient); Texas Children's Hospital, Houston, Texas (one patient); and Yale-New Haven Medical Center, New Haven, Connecticut (one patient). A questionnaire addressing the patients' clinical course and follow-up was given to each center to complete.

Standard methods for calculation of the echocardiographic shortening fraction (SF) were used (left ventricular end-diastolic dimension—left ventricular systolic dimension/left ventricular end-diastolic dimension). Numerical results are expressed in the text as the mean ± SD.

RESULTS

In Utero Course

Congenital heart block was diagnosed in utero in 12 infants. The mean gestational age of clinical presentation was 26.3 ± 6.3 weeks, age range 18 to 37 weeks. Nine fetuses were female and three were male. A pericardial effusion was visualized on fetal ultrasound in six of 12 fetuses. Left ventricular function was normal in all. Four patients received medical therapy in utero: dexamethasone (two patients), terbutaline (one patient), and betamethasone (one patient). In none did the degree of AV block improve. Pericardial effusion improved or resolved in two of two patients with preexisting effusions. The heart rate in utero averaged 49 ± 7 beats/min (Table 1).

At the time of diagnosis of CHB, 13 mothers were asymptomatic, one had Sjogren's syndrome, and two had systemic lupus erythematosus.

Perinatal Period

A detailed clinical and laboratory evaluation of each infant was performed postnatally. A rash consistent with neonatal lupus was detected in one newborn. Two neonates had

Table 1. Presence of Heart Disease and Cardiac Function

Patient	Presence of CHD	Age at CHF	SF: Birth	SF: Worst	SF: Follow-up	Outcome
1	None	Day: 14	0.27	0.18	—	Died
2	None	Month: 6	0.31	0.10	0.29	Alive
3	None	Month: 11	0.34	0.15	0.25	Alive
4	Small PDA/PFO	Month: 12	0.38	0.10	—	Died
5	Small VSD/PDA	Month: 2	0.20	0.11	—	TX
6	ASD, s/p closure	Month: 11	0.30	0.05	0.34	Alive
7	Small PDA/PFO, s/p PDA ligation	Month: 30	0.30	0.05	—	TX
8	None	Month: 10	0.27	0.18	—	TX
9	Small PDA/PFO	Month: 14	0.30	0.10	0.35	Alive
10	Pulmonary stenosis	Month: 21	0.30	0.02	—	TX
11	None	Month: 4	0.54	0.05	—	TX
12	Small PDA	Month: 20	0.45	0.14	—	TX
13	None	Year: 9.3	0.31	0.05	—	TX
14	None	Year: 4.4	0.32	0.06	0.06	TX list
15	None	Month: 9	0.40	0.11	—	Died
16	None	Year: 3.8	0.32	0.06	—	Died

ASD = atrial septal defect; CHD = congenital heart disease; EFE = endocardial fibroelastosis; PDA = patent ductus arteriosus; PFO = patent foramen ovale; SF = shortening fraction; TX = cardiac transplantation.

Table 2. Pacemaker Implantation (Age at and Mode of); and Average Heart Rate (BPM) (Prior to and After)

Patient	Age at PM Insertion	Pacing Mode	Heart Rate: In Utero	Heart Rate: Prior to PM Implantation	Heart Rate: After PM Implantation	Ventricular Pacing Lead Location
1	Day: 1	DDD	50	55	155	RV: inferior
2	Day: 1	DDD	35	40	130	RV: inferior
3	Day: 1	DDD	55	55	140	RV: inferior
4	Day: 2	DDD	55	55	125	RV: inferior
5	Day: 1 and 10	VVI, DDD	40	45	130	RV: inferior
6	Day: 1	DDD	50	52	140	RV: inferior
7	Month: 7 and 25	VVI, DDD	55	65	125	LV: high lateral
8	Day: 1	VVI	45	45	100	RV: inferior
9	Day: 4	DDD	50	50	120	LV
10	Day: 1	VVI	60	45	120	RV: inferior
11	Day: 3, and Month: 7	VVI, DDD	45	50	160	RV: inferior
12	Day: 1	VVI	NA	48	110	RV: inferior
13	Day: 1	DDD	NA	58	120	RV: inferior
14	Day: 7	VVI	NA	50	100	RV: inferior
15	Day: 2	DDD	50–55	50	80	RV: inferior
16	Day: 4	DDD	NA	45–48	80	RV: inferior

DDD = dual chamber pacing mode; LV = left ventricle; NA = not available; PM = pacemaker; RV = right ventricle; VVI = single-chamber ventricular pacing mode.

mildly elevated hepatic transaminases and thrombocytopenia. Congenital heart disease was evident in seven infants: patent foramen ovale/small atrial septal defect with a small patent ductus arteriosus (three patients), a tiny ventricular septal defect and small patent ductus arteriosus (one patient), an atrial septal defect requiring surgical closure (one patient), a moderate to large sized patent arteriosus requiring surgical ligation (one patient), and pulmonary valve stenosis requiring balloon angioplasty (one patient).

Left ventricular function was assessed by 2D echo and was found to be normal in 15 newborns (Table 1). The average SF was 34 ± 7%. Left ventricular function was decreased in one patient. The SF in this infant was 20%.

Because of concern over slow heart rates, a cardiac pacemaker was implanted in all 16 patients (Table 1). Pacemaker implantation occurred on day of life 1 (eight patients), day of life 2 (two patients), day of life 3 (one patient), day of life 4 (two patients), day of life 7 (one patient), day of life 10 (one patient) and at seven months (one patient). The mode of pacing was dual chamber in ten patients and single chamber (VVIR) in six patients (Table 2).

The heart rate prior to pacemaker implantation was 51 ± 6 beats/min (Table 2). Following pacemaker implantation, the heart averaged 121 ± 23 beats/min. The rhythm was predominantly atrial sensed-ventricular paced in those patients with dual-chamber pacemakers. The ventricular pacing lead was placed near the inferior right ventricle in 14 of 16 patients. In two patients the ventricular pacing lead was placed on the left ventricle.

Serologic findings of infants with CHB. Ten of 16 patients had serologic findings consistent with NLS, anti-SSA (Ro) antibody was positive in seven infants and anti-SSB (La) antibody was detected in five newborns. Serologic findings were negative in three patients and unknown in three patients. No consistent immunoblot pattern of antibody profile was evident. Anti-48 KD (SSB/La) antibody was observed in four of five patients tested, anti-52 KD (SSA/Ro) antibody was noted in five of five patients, and anti-60 KD (SSA/Ro)-antibody was found in five of five tested specimens.

Postnatal clinical course. Thirteen infants developed symptoms of congestive heart failure between two weeks and 30 months of age, mean age = 11.6 ± 8.3 months, associated with depressed left ventricular function. At the time of clinical presentation, nine infants had symptoms or signs of an upper respiratory tract infection, two with otitis media. One infant had a respiratory syncytial virus infection. Mean left ventricular shortening fraction was 10 ± 5% (Table 1). All patients were treated with positive inotropic agents and diuretics. Three patients developed clinical deterioration of cardiac function slightly later in life (between 3.75 and 9.3 years, mean age 5.8 ± 3.0 years). At the time of clinical presentation, two of the three older children presented with symptoms or signs of an upper respiratory tract (n = 1) or gastrointestinal infection (n = 1). Mean left ventricular shortening fraction was 9 ± 5%.

Myocardial biopsy or histologic examination of the explanted heart revealed the following: myocyte hypertrophy in 11 of 16 patients, interstitial fibrosis in 11 of 16 specimens, and myocyte degeneration in two subjects. Immunoflorescent studies for antibody, immune-complex or complement deposits were unrevealing in seven patients. In no specimen was an active inflammatory infiltrate detected (Table 3).

During follow-up, four infants died from congestive heart failure and low cardiac output. The ages at death were one month, nine months, 18 months and 4.5 years. Seven patients required cardiac transplantation. The ages at transplantation ranged from nine months to ten years (mean age was 37 ± 38 months). One patient was awaiting transplantation. Myocardial function recovered in four patients. The

Table 3. Histologic Findings

Patient	Histologic Findings			
	Myocyte hypertrophy	Fibrosis	Cellular degeneration	Immunofluorescence
1	−	+	−	−
2	+	+	−	−
3	+	−	−	−
4	+	+	−	−
5	+	+ (EFE)	−	ND
6	+	+	−	ND
7	+	+ (EFE)	−	ND
8	−	+	−	ND
9	+	+	+	ND
10	+	+ (EFE)	−	ND
11	+	+ (EFE)	+	ND
12	+	−	−	−
13	−	−	−	−
14	+	+	−	−
15	−	−	−	ND
16	−	−	−	ND

EFE = endocardial fibroelastosis; ND = not done; + present; − absent.

recovery shortening fraction in these subjects was 31 ± 5% (Table 1).

Each institution was surveyed as to the number of new patients presenting each year with congenital complete AV block (average was between one and two patients/year). The patients enrolled in this study presented at the participating institutions between 1984 and 1999. We therefore approximated the incidence of development of dilated cardiomyopathy in infants with congenital complete AV block to be between 5% and 11%.

DISCUSSION

In the modern era, CHB generally has an excellent prognosis. Some patients have survived to their 40's or even 60's without pacing (6,7). In rare isolated cases, AV conduction has spontaneously returned to sinus rhythm (8,9). Groves et al. recently reported their experience with the longitudinal follow-up of 36 fetuses detected in utero with CHB (4). These authors noted no deaths beyond the neonatal period. Previous reports of death in early infancy were difficult to interpret, given that the majority of the deaths were secondary to congestive heart failure in the setting of bradycardia, i.e., most of these patients failed to receive a pacemaker or may have had coexistent congenital heart disease. Our study highlights an unusual and rare observation that has been underappreciated, i.e., the development of severe cardiomyopathy despite early pacemaker implantation (median age was the first day of life). Two similar cases had previously been reported (10).

Possible risk factors. The obviously small number of patients available for study limited the power of our analysis; however, no consistent finding in the clinical history or evaluation seemed to predict the development of cardiomyopathy. Analysis of serologic findings and the immunoblot patterns failed to reveal differences that would predict the development of a cardiomyopathic state. Waltuck et al. (2) reported similar results in attempting to define specific immunoblot patterns that distinguished affected versus nonaffected infants (complete AV block) born to anti-SSA (Ro) or anti-SSB (La) positive mothers.

On histologic evaluation, the presence of hypertrophy and interstitial fibrosis was noted in either myocardial biopsy specimens or on the explanted heart. Prior pathologic reports have made similar observations. Lev et al. (11) reported endocardial fibroelastosis and fibrosis in the right and left ventricle in seven cases. Their findings appeared not to be restricted to the conduction system but involved working ventricular myocardium. On rare occasions, scattered foci of mononuclear inflammatory cells were detected. Litsey et al. (12) observed mild endocardial fibroelastosis in several areas of the heart, along with widespread dystrophic calcification. Lee et al. (13) observed IgG and complement deposition in all cardiac tissues examined, not only in the myocardium but also in and around the conduction system. Several other case reports further support the concept of transient myocarditis that evolves into fibroelastosis (14–16). At the time of clinical presentation 11 of our 16 patients had an upper respiratory/gastrointestinal infection, which might have reactivated a previously dormant inflammatory process.

Cardiac damage consisting of myocarditis, inflammation, and fibrosis of the conduction system has similarly been observed in 60% to 70% of adult patients with polymyositis associated with antibodies to tissue ribonucleoproteins (17). Anti-SSA (Ro) antibodies are detected in up to 60% of these patients.

Sustained rapid ventricular rates, as has been noted during incessant forms of supraventricular tachycardia, may elicit a tachycardia-induced cardiomyopathy (18). All of our infants underwent early pacemaker implantation for "slow"

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heart rates. Concern may be raised that the increased rate that followed pacemaker implantation may have provoked a form of tachycardia-induced cardiomyopathy. Histologic studies by Karpawich et al. (19,20) in a chronic canine model of cardiac pacing, as well as in children with congenital AV block paced from the right ventricular apex, have revealed dystrophic changes in myocardial structure that may contribute to a pacing-induced cardiomyopathic state. We feel that such was not the case in our patient population, because one-quarter of the patients clinically improved without any alteration in their pacing mode or rate. Furthermore, the heart rates after pacemaker implantation were within the normal range for this age group.

Previous studies have assessed the outcome of pediatric patients with dilated cardiomopathy (21–23). These studies have revealed that approximately one-third of patients die, one-third improve clinically but continue with residual hemodynamic dysfunction and one-third recover completely. As mentioned earlier, our patient population followed a similar trend.

Study limitations. Several limitations to our study need to be specified. Seven of the 16 patients had congenital heart defects with three requiring intervention. Either the presence of the congenital heart disease or the intervention required for its management might have contributed to the ventricular dysfunction in these patients. The surgical or balloon angioplasty techniques required for treatment of the congenital heart defects have rarely been reported to result in the degree of ventricular dysfunction experienced by our patient population. Four patients were paced in the VVIR mode, which could conceivably have contributed to their congestive heart failure symptoms. Single-chamber ventricular pacing, although less than ideal, is usually well tolerated in this age group and is clinically performed at many centers without adverse outcome.

Conclusions. We conclude that despite early institution of cardiac pacing, some infants with CHB will develop cardiomyopathy. Patients with CHB require close follow-up, not only of their cardiac rate and rhythm, but also of their ventricular function, particularly during the first few years of life. Late-onset cardiomyopathy in patients with CHB may represent a sequela of in utero autoimmune or postnatal reactivation myocarditis. One must also consider the possibility that early intervention with cardiac pacing may produce a tachycardia-induced cardiomyopathy.

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